Tab 113

DEPARTMENT OF HEALTH AND HUMAN SERVICES — Public Health Service

Food and Drug Administration
College Park, MD 20740

MAY 14 2003

Note To: The Commissioner

Subject: Special Government Expert Reviews of the Boozer-Daly study

Dr. McClellan,

As part of your ongoing deliberations regarding dietary supplements containing ephedrine alkaloids with and without caffeine, I want to inform you of a review that Ladd Wiley and I negotiated with the "industry" and study investigators relating to dietary supplements containing ephedrine alkaloids with and without caffeine. This negotiation took about 18 months and was agreed to by Dr. Carol Boozer through Wes Signer of Hymen, Phelps and McNamara, who represents the Ephedra Council and Metabolife International, Inc. The law firm of Patton Boggs also played a role in this. The agreement we reached involved two principal items: (1) the names of the outside experts and (2) the results of their reviews would be shared with Dr. Boozer and Wes Signer before the government made them public. We have now received three of the four contracted reviews. The reviewers are:

Dr. Richard L. Atkinson – Director, Obesity Institute, MedStar Research Institute

Dr. Mark A. Espeland – Wake Forest University School of Medicine, Department of Public Health Sciences

Dr. Alan T. Hirsch – University of Minnesota Medical Center, Minnesota Vascular Disease Center

Dr. Norman M. Kaplan – University of Texas Southwestern Medical Center at Dallas

The main points I gather from the three reviews are as follows:

- The study was generally well-designed and conducted.
- The formulation may or may not represent what is being marketed.
- The controls, subject selection, exclusion criteria, and monitoring do not represent real world use conditions.
- The product seems to offer some short term weight loss.
- The product should only be used with the monitoring of a learned intermediary.

- One expert believes the study was seriously compromised due to some mix-up in the active and placebo preparations.

I have attached the Boozer-Daly publication which the industry has and continues to use as the "gold standard" study proving safety of this product, along with the charge sent to the reviewers and their respective reviews. I believe we now need to decide upon the next steps regarding what to do with this reviews. I will await your instructions.

Thank you,

/s/
Charles W. Prettyman

Attachments
Boozer-Daly publication
Charge to reviewers
Reviews

cc:
Joseph A. Levitt
Daniel Troy
William Hubbard
Ladd Wiley

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: July 14, 2003

From: Mark B. McClellan, Commissioner of Food and Drugs MM

Subject: Response to May 14, 2003 Memorandum

To: Charles Prettyman, Center for Food Safety and Nutrition

This memorandum responds to your memorandum, dated May 14, 2003, informing me of your efforts to facilitate access to, and obtain peer review of, the Boozer-Daly study relating to potential health effects associated with usage of ephedrine alkaloids. Your memorandum was received in the Office of the Executive Secretary on May 22, 2003, but was not brought to my attention until July 11, 2003. I apologize for the delay in responding; in the future to expedite review and ensure prompt attention, please transmit such requests through the Center Director. Your memorandum raises several questions that are outlined below upon which I am requesting that you provide additional information as promptly as possible in order for the Agency to determine how most appropriately to proceed with its consideration of the Boozer-Daly study and the peer reviews conducted by the outside experts identified in your memorandum.

As you know, we have been diligently pursuing efforts to complete our review of the scientific evidence regarding usage of ephedrine alkaloids in order to determine whether and how, employing the best available scientific data, to proceed with additional regulatory steps to address the public health concerns that have been identified. In addition, we are pursuing significant new enforcement actions against manufacturers of dietary supplements containing ephedrine alkaloids that were marketing the product using unsubstantiated, false or misleading claims, primarily relating to sports or athletic performance. In addition, we have continued our aggressive enforcement initiative to target dietary supplements that are marketed as street drug alternatives. These and other enforcement actions have substantially altered ephedra marketing in the U.S., and I hope you will continue to pursue an aggressive enforcement strategy. Furthermore, on March 5, 2003, based in part on a comprehensive analysis of the available scientific data and adverse events reports regarding health effects associated with ephedra conducted by the Rand Corporation under contract to the National Institutes for Health, the Agency issued a proposed rule to change the labeling for ephedrine alkaloids by adding substantial new warnings about their potential health effects. In the rulemaking, we also sought and have received comments on how the Agency could proceed, in accordance with the Dietary Supplements Health and Education Act (DSHEA) to potentially further restrict access to ephedra containing dietary supplements that pose a significant or unreasonable risk to public health. I appreciate your efforts and those of your colleagues in the process of reviewing the 16,000 public comments as quickly as possible.

Although I am confident that the Agency has worked and continues to work expeditiously towards a public health outcome for dietary supplements containing ephedrine alkaloids that protects the public health to the fullest extent available under the law, your memorandum raises certain issues about which I believe it is imperative to receive clarification prior to proceeding with further consideration of the outside peer reviews regarding the Boozer-Daly study. I recognize the

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: July 16, 2003

From: Charles W. Prettyman, Center for Food Safety and Applied Nutrition

Subject: Response to your July 14, 2003 Memorandum

To: Mark B. McClellan, Commissioner of Food and Drugs

I am responding to your request for clarification on issues raised in my previous memorandum. About two years ago the Department and members of the Agency began a series of meetings and discussions with Drs. Boozer and Daly and attorneys representing members of the industry marketing dietary supplements containing ephedrine alkaloids. These activities were initiated because of the importance the industry placed on the six-month Boozer-Daly study as confirmation of the safe use of these products for weight loss. It was the only controlled study of any size and duration we were aware of and remains so to this day. As you stated in your memo to me, it is a very important piece of our overall evaluation.

The Department and members of the Agency spent nearly eighteen months trying to obtain the "raw data" from this study with little success. Dr. Boozer and counsel raised concerns over pre-publication public release of the study while it was under peer review for the International Journal of Obesity and concerns that the agency was trying to somehow discredit Dr. Boozer. Both the Department and the Agency went to great lengths to assure Dr. Boozer that our sole purpose was to use all of the best available information to reach a scientifically sound decision regarding the safe use of these products and her study was seen as a pivotal piece in the process. This was routine procedure for th FDA. After about eighteen months, the Department was able to reach an agreement through Mr. A. Wes Signer, Hyman, Phelps and McNamara, who was representing both the Ephedra Council and Dr. Boozer as to how Dr. Booz could release data tapes to the agency. I was asked to obtain the names of experts in the fields of Cardiovascular Medicine, Pharmacology, Neurology, and weight loss from within the FDA and the NIH. I was given approximately 6 – 8 names of experts in these fields and I provided those names to the Department. Those names were shared with Mr. Signer and four experts were identified to perform a review of the Boozer-Daly study. Again, we selected the experts and allowed input through Mr. Signer of any potential objections. I then took these names to the CFSAN sta who normally deal with Special Government Employees, peer reviewing, and advisory committees and asked them t follow routine procedures for engaging their services. Conflict of interest matters were addressed per standard protocol and a charge was given as to what questions we wanted addressed, the timeframe for this work to be completed, and compensation. We have full documentation for all of this. The questions were shared with Mr. Sign but were not changed – we simply shared them.

As I indicated in my previous memo three of the four reviews have been completed. The fourth will not be performe due to time constraints. All 3 reviews are consistent in their conclusions that the study was basically conducted well but it is not sufficient to address the safety of these products as they are used in the marketplace by the population at large. One reviewer was also concerned over the validity of the results due to labeling mix-up between active and placebo. These conclusions are very consistent with an internal review performed by CDER's Metabolic-Endocrine division. Personally, I do not see the need for additional outside peer review. I have no reason to believe these reviewers were biased in any way and did provide us an independent and impartial review.

tireless work of so many of the Agency's staff on this project and greatly appreciate their dedication to assisting the Agency in obtaining the best available scientific data regarding ephedrine alkaloids, including the efforts you and have undertaken to acquire adverse event reports associated with the use of such products. I also acknowledge the role of the Boozer-Daly study in assembling this scientific database and I greatly appreciate your efforts to obtain it. However, based upon my review of your May 14, 2003 memorandum, I believe it is important to request that you provide specific clarifications in order to be assured that the outside reviews that were conducted of the Boozer Daly study were unambiguously consistent with all of the requirements for appropriate scientific peer review of this nature.

In order to assist me in more fully understanding the nature of the negotiations with non-governmental parties outlined in your memorandum, please respond to the following questions: describe in more detail how the four outside expert reviewers of the Boozer Daly study identified in your May 14, 2003 memorandum were selected by the Agency; in particular, indicate whether any non-governmental parties were involved in the identification and selection process for the outside peer reviewers, and what role, if any, such non-governmental parties had in the selection of the outside reviewers; indicate whether the four outside experts identified in your memorandum underwent all necessary and qualifying conflict of interest evaluations to ensure their independence and impartiality; describe the results of any such evaluations; and finally, please indicate whether you have any reason to call into question the independence or impartiality of the outside reviews conducted by the experts identified in your May 14, 2003 memorandum, and whether you would recommend that the Agency empanel additional outside peer reviewers to further evaluate the study design and results of the Boozer-Daly study prior to moving forward with deliberations as part of the rulemaking process.

Thank you for informing me of your efforts to negotiate access to the Boozer Daly study. In order to clarify ambiguities raised by your May 14, 2003 memorandum, I would greatly appreciate your prompt response to the inquiries identified above.

I hope this is responsive to your request and can supply you with all of the material as needed.

/s/
Charles W. Prettyman

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

CONSULT

FROM: Patricia Beaston-Wimmer, M.D., Ph.D.
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products

THROUGH: David Orloff, MD Director, DMEDP

TO: Buddy Prettyman, Senior Policy Advisor, CFSAN

Re: Review of Boozer-Daly article for ephedrine and caffeine

DATE: January 10, 2003

This consult reviews the background for the safety issues raised by the use of ephedrine and caffeine, either as pure drug or as herbal supplements, by the general population for weight loss and focuses on a single article frequently cited in the literature to demonstrate the safety of the combination.

Background

Ephedrine and caffeine are both available in the USA as over-the-counter drugs and as components of nutritional supplements. However, concerns have been raised regarding the safety of the ephedra alkaloids as a class. Two studies examining adverse events related to the use of ephedra alkaloids and phenylpropanolamine (PPA) were reported in the New England Journal of Medicine[1]. The adverse events appeared to be greater when these drugs were used in dietary supplements for weight loss or increased physical performance then when used as components of cough and cold or asthma medications. The information resulted in interdiction of PPA as a component of over-the-counter drugs. Studies and discussions regarding the safety of ephedra alkaloids are ongoing.

To date 1783 adverse event (AE) reports have been filed with the Agency involving the use of ephedra. An audit of Metabolife, perhaps the largest marketer of ephedrine containing supplements, revealed more than 13,000 unreported adverse events. Unfortunately the information in the majority of these reports is minimal. An external review (by the Southern California Evidence Based Practice Center, RAND) of the 1783 filed AEs and the current literature related to the use of ephedrine and caffeine is in progress.

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[1] Haller, C.A. and Bonowitz. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. N Engl J Med. 2000 Dec 21;343(25):1833-8.
Kernan, W.N.et al. Phenylpropanolamine and the risk of hemorrhagic stroke. N Engl J Med. 2000 Dec 21;343(25):1826-32.

Drugs/Herbals at Issue

Ephedrine is a non-selective adrenergic agonist that also enhances release of norepinephrine from sympathetic neurons. The drug stimulates heart rate, cardiac output, and peripheral resistance and usually increases blood pressure. Adverse events are related to its sympathomimetic effects - dizziness, tremor, irritability, insomnia, dry mouth, and headache.

Caffeine is a methylated xanthine and is related to the xanthines theophylline and theobromine. These agents stimulate cardiac muscle, relax smooth muscle (hence their previous use in asthma treatment), and act on the kidney to promote diuresis. Caffeine also acts as phosphodiesterase (PDE) inhibitor that potentiates the activity of ephedrine. Adverse events are related to stimulation of the cardiovascular and central nervous system.

The putative beneficial effect of ephedrine plus caffeine products as weight loss agents is based on their ability to suppress appetite and increase thermogenesis. Whether these compounds individually or in combination are responsible for the myocardial infarctions and strokes described in the adverse events is not known but is consistent with the known cardiovascular and central nervous system effects of both compounds.

In the absence of large controlled clinical trials it is extremely difficult to quantitate the risk associated with the use of ephedrine with or without caffeine. However, one paper by Boozer et al. is widely cited in support of the safety and effectiveness of ephedrine in combination with caffeine to treat obesity. Although the Boozer study appears to be well executed, there are several important differences between its design relative to completed and ongoing ephedrine plus caffeine trials — the latter conducted under IND in this Division. An outline and discussion of this article follows.

Article Reviewed

HERBAL EPHEDRA/CAFFEINE FOR WEIGHT LOSS: A 6-MONTH RANDOMIZED SAFETY AND EFFICACY TRIAL. Boozer et al., Int. J. Obesity (2002) 26:593-604.

Study design

This is a 6-month, placebo-controlled, double-blind, randomized clinical trial. Subjects were recruited through advertisements in local newspapers and by flyers and were screened by phone interview. Treatment consisted of either an herbal ephedrine product with caffeine or placebo, with both groups receiving diet and exercise recommendations.

Inclusion/exclusion criteria:

18 to 80 years old
BMI ≥ 25 and ≤ 40 kg/m^2
Diabetics allowed if not on medications and $HbA_{1c} \leq 7.8\%$

Caffeine intake < 500 mg/day
Sitting BP < 140/90 mmHg and.
Normal 24-hour Holter monitor[2] and ambulatory blood pressure monitoring (ABPM) mean 24 hour SBP < 139 mmHg or DBP < 87 mmHg on two occasions
No regular medications except for oral contraceptives, thyroid hormone, 'hormone replacement therapy'. No aspirin use.

Treatment:

Diet ≤ 30% calories from fat
Moderate exercise (i.e. walk 30 min/day) 3 times per week
2 tablets each of ephedrine alkaloids (15 mg total ephedrine alkaloids, each tablet) and caffeine (32 mg each tablet)
Total daily dose 90 mg ephedrine alkaloids and 192 mg caffeine.

Safety Monitoring:

Weeks 1-4 – 24 hour Holter monitor and APBM weeks 1, 2 and 4
Weeks 5-24 – adverse event inquiry and vital signs Q 4 weeks
Weeks 12+24 – blood work, anthropomorphics, EKG

Statistical Plan:

Statistical analyses were designed on an intent-to-treat basis. Power calculations were primarily concerned with the possibility of adverse events. A primary efficacy variable was not defined. Efficacy measurements included change in weight, body fat mass, waist and hip circumferences, and lipid levels.

Results

Population:

Of the 284 subjects deemed eligible by phone screen, 45 chose not to participate, 15 were found ineligible due to violations of inclusion requirements, 8 were non-compliant with the protocol, and 31 were ineligible for medical reasons that were exclusionary. One hundred sixty-seven subjects were eligible for randomization. Eight subjects were found to be ineligible after randomization, leaving 159 subjects eligible by entry criteria. Data were not reported for all randomized subjects. The following table summarizes the demographic characteristics of the randomized subjects:

[2] Holter data and EKGs of subjects with multiform or multifocal ventricular events were reviewed by the study cardiologist prior to admission.

Baseline Characteristics of Randomized Subjects:

Baseline Characteristics	Placebo N = 84	Herbal caffeine/ephedrine N = 83
	n (%)	n (%)
Gender		
male	12 (14)	18 (22)
female	72 (86)	65 (78)
Race		
Caucasian	59 (70)	57 (69)
African-American	13 (15)	9 (11)
Hispanic	6 (7)	10 (12)
Indian, Asian, Other	5 (6)	6 (7)
	x ± S.D.	x ± S.D.
Age (years)	46.0 ± 12.2.	44.5 ± 12.4
Weight (kg)	88.1 ± 14.8	87.9 ± 13.8
Body Mass Index (kg/m^2)	31.7 ± 4.0	31.8 ± 4.4

Comment: The two groups were well-matched for baseline characteristics.

Efficacy endpoints:

The following table provides the results of the efficacy analyses.
(From Table 2)

Anthropomorphic Endpoints Change from Baseline to Endpoint (LOCF) (mean ± SD)	Placebo [n]	Herbal caffeine/ephedrine [n]	p
Body Weight (kg)	-2.6 ± 3.2 [69]	-5.3 ± 5.0 [69]	<0.001
Body Fat Mass (kg)	-2.7 ± 2.8 [38]	-4.3 ± 3.3 [39]	0.02
Waist Circumference (cm)	-2.0 ± 6.0 [48]	-6.0 ± 5.0 [48]	0.005
Hip Circumference (cm)	-4.0 ± 4.0 [48]	-6.0 ± 5.0 [48]	0.018

In addition to the statistically significant reductions in body weight, fat mass, and waist and hip circumferences in the caffeine/ephedrine vs. placebo groups, there were statistically significant decreases in LDL-cholesterol and increased HDL-cholesterol in the caffeine/ephedrine group compared to placebo. No significant differences were found in total cholesterol or triglycerides (Table 5). (Percent change from baseline was not reported.)

Safety endpoints

The table below provides the changes in blood pressure and heart rate.

(From Table 2)

Safety Endpoints Change from Baseline to Endpoint (LOCF) (mean ± SD)	Placebo [n=69]	Herbal caffeine/ephedrine [n=69]	p
Systolic BP (mmHg)	0 ± 11	-1 ± 9	0.313
Diastolic BP (mmHg)	0 ± 8	<1 ± 8	0.928
Heart Rate (bpm)	-3 ± 9	4 ± 9	<0.001

Comment: Although the authors state that the data are based on intent-to-treat (ITT) and last-observation-carried-forward (LOCF) analyses, the number of subjects reported for the above endpoints is not representative of the number of subjects randomized. The authors do not explain why these 29 subjects (15 placebo and 14 herbal) were excluded from the analyses.

The source of the blood pressure and heart rate data (i.e., cuff or ABPM) presented in the table above is not clear from the text. The average values reported do not match those from either the Holter monitor data (Table 4; n not reported) or the ABPM data (Table 3; n=67 caffeine/ephedrine, n=66 placebo) – neither of these tables report change from baseline to endpoint and no table provides ranges of values. The ABPM data showed statistically higher average blood pressure measurements at week 4 in the caffeine/ephedrine treated subjects compared to placebo treated subjects for both the '24-hour average' and 'night (midnight-6:00 am)' periods.. (For the reader's convenience, Table 3 is reproduced in the Appendix.) The number of measurements taken over any time period was not reported.)

Adverse events and withdrawals

For patients withdrawn from the study, either by choice or by investigators, there were no statistically significant differences reported by AE (Table 7). The number of subjects reporting AEs not leading to withdrawal was not provided in the paper. However, as shown in Table 6 (reproduced below), more subjects ($p < 0.5$) reported AEs in the herbal group compared to placebo for almost every parameter in both the acute and chronic phases.

Table 6 LOCF analysis of self-reported symptoms

	Symptom								
	Acute phase					Chronic phase			
	B	W1	W2	W3	W4	B	M1	M3	M6
Constipation	—	H > P**	H > P**	H > P**	—	—	—	—	—
Diarrhea	—	—	—	—	—	—	—	P > H*	P > H*
Difficulty concentrating	H > P*	—	—	—	H > P*	H > P*	—	H > P*	—
Dizziness	H > P*	H > P*	H > P*	—	H > P*	—	—	—	—
Dry mouth	—	H > P*	H > P*	H > P*	H > P*	—	H > P**	H > P**	H > P**
Heartburn	—	H > P*	H > P*	H > P*	H > P*	—	H > P**	H > P**	H > P*
Insomnia	—	H > P*	H > P*	H > P*	H > P*	—	H > P**	H > P**	H > P**
Anxiety	—	H > P*	—	—	—	—	—	—	—
Upset stomach	—	H > P*	H > P*	—	—				

Acute phase: B, baseline (prior to treatment); W1, W2, W4, weeks 1, 2 and 4 after treatment with either herbal (H, $n = 69$) or placebo (P, $n = 68$).
Chronic phase: B, baseline (prior to treatment); M1, M3, M6, months 1, 3 and 6 after treatment with either herbal (H, $n = 66$) or placebo (P, $n = 70$).
*$P < 0.05$; **$P < 0.01$ (repeated measures ANOVA of group by time interaction, followed by pair-wise t-tests).
There were no differences between treatment groups at any time point for blurred vision, chest pain, headache, irritability, nausea or palpitations.

Withdrawals: 17 subjects (20%) from each group withdrew during Weeks 1-4 and 20 (24%) herbal and (26) 31% placebo during Weeks 5-24.

Comment: Individual subject data reporting the reason for withdrawal were not provided in the text. It is difficult to determine the number of subjects who withdrew from the study because of 'choice' versus because of an 'adverse event'. However the numbers reported in Table 7 suggest that more subjects in the placebo group withdrew by choice, whereas more subjects in the caffeine/ephedrine group withdrew because of adverse events.

Summary

The Boozer study appears to be the most comprehensive and well-conducted study of caffeine/ephedrine published to date. The results of this trial indicate that treatment for up to 6 months with 30 mg TID ephedrine alkaloids plus 64 mg TID caffeine results in an average placebo-subtracted weight loss of 2.7 kg (this is roughly equivalent to the average placebo-subtracted weight loss observed with sibutramine and orlistat following 6 months of treatment). While there were improvements in serum levels of LDL and HDL cholesterol in the ephedrine/caffeine group relative to the placebo group, blood pressure and pulse rate, as measured by 24-hour ABPM, increased in the drug- vs. placebo-treated group. Given the drug combination's sympathomimetic activity, this pressor effect is not surprising, and in fact, is the basis for the ongoing concern regarding the safety of these two compounds.

As regards relying on the results of the Boozer study to assess the safety of the ephedrine/caffeine products that are available over-the-counter, a number of factors should be kept in mind.

First, the doses of both the ephedrine and caffeine differ. The Boozer study used an herbal mixture, not pure drug. Herbal ephedrine usually contains 4 isomers of ephedrine with 1R,2S-Ephedrine having the greatest potency of the four. The amount and distribution of the ephedrine alkaloids in any herbal preparation is dependent on the season the plants are harvested and on the species of ephedra used. Therefore, although the dose for the ephedrine alkaloids is higher (30 mg TID) in this study than the dose

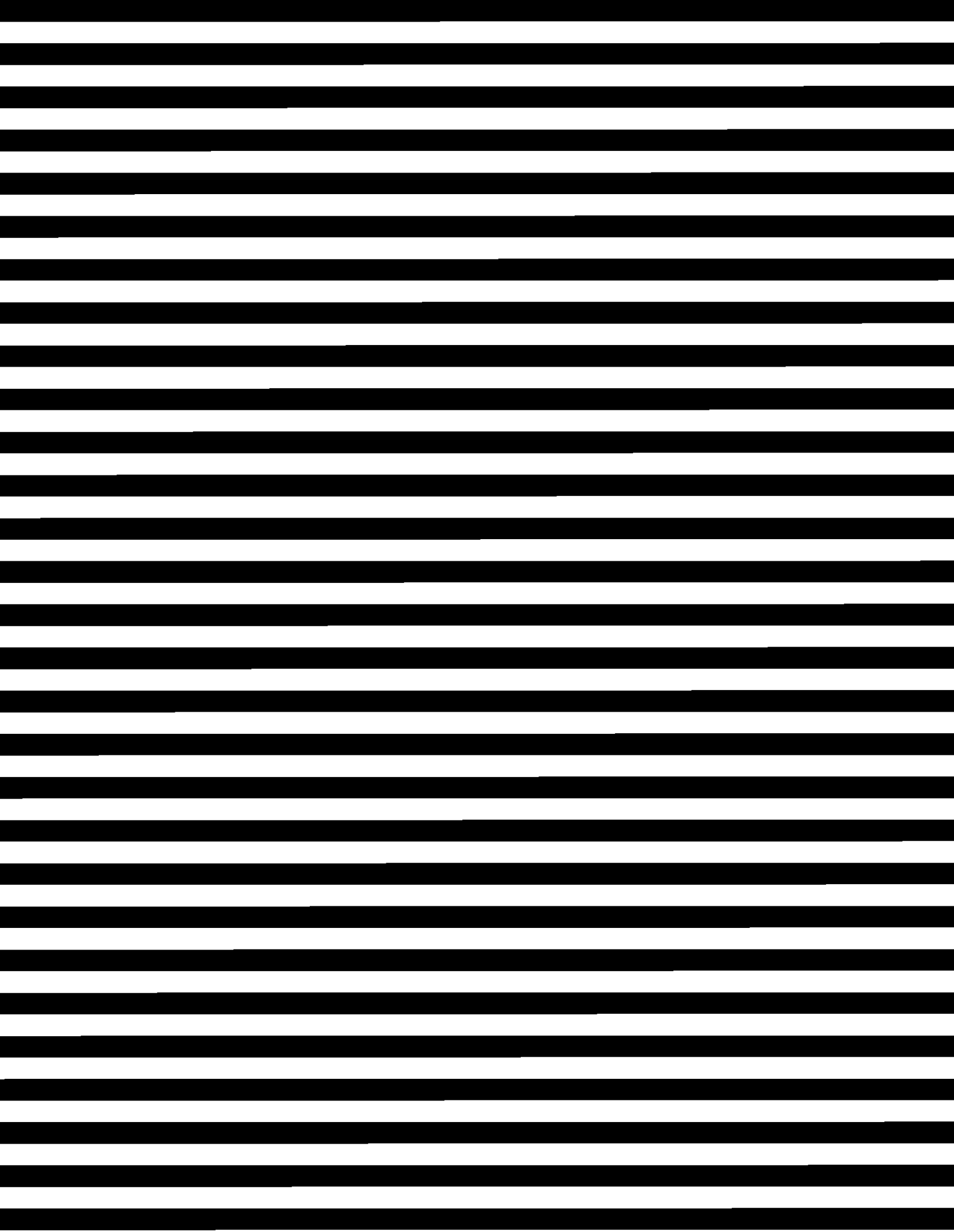
used in other studies of ephedrine (24-25 mg TID of pure drug), the material used in the Boozer study may in fact have less adrenergic activity. The caffeine doses are also smaller (64 mg TID) than those used in other studies (100-200 mg TID). Methylxanthines, caffeine in this case, act to potentiate the effects of ephedrine. Therefore, lower doses of caffeine may not produce the same total effect in the combination. Furthermore, subjects were not allowed to use aspirin during the study, a commonly used analgesic and CAD prophylactic that also potentiates the activity of ephedrine. Additionally, because there is no requirement that the herbal preparations report the exact content of the individual ephedra alkaloids, it would be impossible to compare different preparations, or even different lots of product, making general comments regarding relative safety and efficacy difficult, if not impossible.

Second, the population used in the Boozer study is not necessarily representative of the general obese population in the U.S. This was a very highly screened population of patients who had to have to normal Holter monitor studies in addition to meeting other inclusion criteria. Additionally, subjects did not have to be obese to enter the study - inclusion criteria of BMI ≥ 25 and ≤ 40 kg/m^2 whereas the general entry criterion for obesity drugs seeking registration is a BMI of ≥ 30 kg/m^2 or 27 kg/m^2 with comorbid conditions. In the Boozer study, subjects with hypertension, dyslipidemia, etc. were excluded from participation. The average BMI of subjects in this study was approximately 32 kg/m^2, suggesting that many of the subjects would not have met the inclusion criteria for the majority of studies submitted in support of FDA approval. Additionally, the study is small compared to those used to support U.S. registration of a weight loss agent. Well over 1000 subjects participated in the phase 2 and 3 studies of sibutramine and orlistat — two recently approved obesity drugs.

Third, interpretation of both adverse event reports and vital sign data is limited by the manner in which the data are presented/displayed in the publication. For example, although the number of patients withdrawn from the study secondary to adverse events was reported, the number of adverse events was not reported for all subjects. In the article, Table 6 provides a summary of all adverse events showing which group reported more adverse events for each parameter. The number of subjects reporting adverse events was not provided, however, according to the table, more subjects ($p< 0.5$) reported AEs in the herbal group compared to placebo for almost every parameter in both the acute and chronic phases.

Vital signs were only reported from Holter monitor and ABPM data. Acute increases in response to treatment could be missed with averaging over time. Furthermore, only the mean and S.D. were reported, preventing an assessment of outliers. To capture acute pressor effects, this Division has required that subjects participating in caffeine/ephedrine studies have their blood pressure and pulse closely monitored during the 3 hours following the first dose.

Fourth, a complete evaluation of the weight loss efficacy of this combination cannot be made from the data presented. Weight loss is reported as group means only. Current FDA guidance on the development of drugs for the treatment of obesity requires that the



percent weight loss from ba[redacted]the treated group is 5% greater (absolute) than that of the placebo group or that[redacted] proportion of treated subject achieve and maintain a 5% weight loss when comp[redacted]e placebo group. In the Boozer study, ephedrine/caffeine-treated s[redacted]t an average of 5.3 ± 5.0 kg compared to the placebo-treated group whic[redacted]average of 2.6 ± 3.2 kg ($p < 0.001$). The clinical significance of this differen[redacted]adequately discussed. Although some improvements in lipid parameters were fo[redacted]e caffeine/ephedrine group compared to the placebo group, the percentage chan[redacted]t reported nor is it apparent that subjects benefited from the change, i.e. move[redacted]igher risk group to a lower risk group, or that there was a correlation between p[redacted]eight loss and change in LDL- or HDL-cholesterol. Additionally, despite the st[redacted]y significant difference in weight loss the ephedrine group had a mean increase[redacted]te of 4 bpm at the end of the 6-month treatment period while the placebo g[redacted]a 3 bpm decrease. Furthermore, although no mean change in blood pressure w[redacted]ed in either group from 'sitting' measurements, there was an increase in average [redacted]ssure measurements at several time periods by ABPM in the caffeine/eph[redacted]ted subjects compared to placebo. Management of hypertension associated w[redacted]y is among the reasons for treating obesity. Failure to lower and possibly increas[redacted]pressure despite the slightly greater weight loss in the caffeine/ephedrine gro[redacted]ts that this method of weight loss is of questionable clinical benefit.

Finally, the description of t[redacted]ment for this study makes it clear that patients could not have self-screened into[redacted]. The screening process was complex and aimed at excluding patient who mig[redacted]med to have undue risks for the adverse cardiac consequences of the drug c[redacted]n. It involved Holter monitoring, ABPM, history and physical exam, all pro[redacted]d analyses that require physicians, medical technology, and support st[redacted]e extent that the entry criteria for the study reflect prudent prescribing guide[redacted]e drug, this fact raises concern for the safe use of this combination without supe[redacted]y a learned intermediary. Subjects were recruited from the general public. Of the[redacted]jects deemed eligible by phone screen, 46 (16%) did not meet entry criteria. A[redacted]l 8 subjects (4 from each group) were dropped after randomization for 'previo[redacted]closed ineligibility,' leaving a total of 54 (19%) who failed screening. It would[redacted]ting to look at the recruitment advertisements used and to have a record of all[redacted]nts to the ads to gage how many respondents were required to obtain the init[redacted]e fact that 19% of subjects failed screening after talking to a trained intervi[redacted]s concerns as to whether the general population can self-select for the safe use[redacted]rugs. Of note, in the Editorial and Guest Editorial that accompany the Booze[redacted]th Drs. Atkinson and Dulloo caution against the use of these drugs without the[redacted]n of a physician.

In conclusion, although v[redacted]t-term studies, including that of Boozer et al., have demonstrated minor to m[redacted]t loss with ephedrine and caffeine compared to placebo, the safety of this[redacted]n, particularly its effect on the cardiovascular system, has not been ade[redacted]ed. Given that this drug combination has the potential to raise blood pr[redacted]pulse, it's reasonable to assume that some individuals who take eph[redacted]caffeine would be at increased risk for

cardiovascular events. The most reliable way to test this hypothesis would be by way of a large, long-term, randomized, controlled trial (i.e., 10,000 obese patients studied for at least 3 years).

APPENDIX – Table 3, Twenty-four-hour ambulatory blood pressure monitor data

Table 3 Twenty-four-hour ambulatory blood pressure monitor data

		24 h average			Day (6:00 am – midnight)			Night (midnight – 6:00 am)		
		Placebo	Herbal	P	Placebo	Herbal	P	Placebo	Herbal	P
SBP (mmHg)	B	118 ± 8	120 ± 8	0.403	120 ± 8	121 ± 8	0.602	108 ± 8	110 ± 9	0.179
	W1	118 ± 8	118 ± 8	0.754	120 ± 9	119 ± 10	0.462	108 ± 10	110 ± 11	0.230
	W2	116 ± 8	118 ± 8	0.133	118 ± 8	120 ± 8	0.251	106 ± 9	111 ± 10	0.005
	W4	116 ± 11	120 ± 9	0.020	118 ± 11	121 ± 8	0.060	107 ± 10	111 ± 10	0.014
	ANOVA	Time × group interaction: $P = 0.016$			Time × group interaction: $P = 0.021$			Time × group interaction: $P = 0.152$		
DBP (mmHg)	B	72 ± 7	72 ± 6	0.887	74 ± 7	73 ± 6	0.252	63 ± 6	63 ± 7	0.991
	W1	72 ± 10	72 ± 7	0.637	74 ± 7	73 ± 6	0.340	64 ± 8	65 ± 8	0.646
	W2	71 ± 10	73 ± 7	0.200	74 ± 7	74 ± 6	0.895	63 ± 7	64 ± 9	0.193
	W4	71 ± 11	75 ± 8	0.036	74 ± 8	76 ± 11	0.251	61 ± 10	65 ± 10	0.015
	ANOVA	Time × group interaction: $P = 0.020$			Time × group interaction: $P = 0.053$			Time × group interaction: $P = 0.066$		
MINSBP (mmHg)	B	95 ± 7	95 ± 8	0.766	98 ± 8	98 ± 8	0.454	98 ± 8	99 ± 10	0.277
	W1	94 ± 9	95 ± 10	0.729	98 ± 11	98 ± 11	0.991	97 ± 10	100 ± 11	0.160
	W2	91 ± 9	95 ± 9	0.030	95 ± 11	99 ± 10	0.035	94 ± 10	99 ± 10	0.004
	W4	93 ± 10	97 ± 10	0.012	96 ± 12	101 ± 10	0.021	96 ± 10	100 ± 11	0.043
	ANOVA	Time × group interaction: $P = 0.008$			Time × group interaction: $P = 0.017$			Time × group interaction: $P = 0.257$		
MINDBP (mmHg)	B	50 ± 6	49 ± 8	0.400	53 ± 7	53 ± 8	0.798	52 ± 7	54 ± 8	0.263
	W1	52 ± 7	49 ± 9	0.116	54 ± 7	54 ± 10	0.819	54 ± 8	55 ± 8	0.695
	W2	51 ± 6	50 ± 10	0.606	54 ± 7	54 ± 8	0.917	52 ± 7	52 ± 9	0.884
	W4	50 ± 7	51 ± 9	0.576	54 ± 8	55 ± 8	0.552	52 ± 7	54 ± 9	0.323
	ANOVA	Time × group interaction: $P = 0.089$			Time × group interaction: $P = 0.868$			Time × group interaction: $P = 0.652$		
MAXSBP (mmHg)	B	143 ± 12	143 ± 11	0.741	142 ± 12	143 ± 11	0.922	119 ± 9	122 ± 11	0.077
	W1	142 ± 13	141 ± 12	0.917	141 ± 13	141 ± 12	0.713	119 ± 12	121 ± 13	0.370
	W2	140 ± 12	141 ± 10	0.591	140 ± 12	141 ± 10	0.835	117 ± 12	121 ± 13	0.046
	W4	140 ± 14	140 ± 13	0.716	140 ± 14	138 ± 21	0.559	118 ± 12	122 ± 12	0.078
	ANOVA	Time × group interaction: $P = 0.941$			Time × group interaction: $P = 0.803$			Time × group interaction: $P = 0.683$		
MAXDBP (mmHg)	B	93 ± 8	93 ± 10	0.969	93 ± 9	93 ± 9	0.991	72 ± 8	73 ± 10	0.859
	W1	94 ± 11	92 ± 8	0.104	94 ± 12	92 ± 7	0.156	75 ± 10	74 ± 7	0.339
	W2	92 ± 8	92 ± 10	0.885	92 ± 8	91 ± 8	0.388	73 ± 9	73 ± 8	0.991
	W4	94 ± 12	93 ± 8	0.576	94 ± 12	92 ± 8	0.295	73 ± 10	76 ± 10	0.044
	ANOVA	Time × group interaction: $P = 0.433$			Time × group interaction: $P = 0.605$			Time × group interaction: $P = 0.059$		
MAP (mmHg)	B	87 ± 6	87 ± 6	0.877	90 ± 6	90 ± 6	0.537	79 ± 6	79 ± 7	0.649
	W1	86 ± 7	86 ± 6	0.452	90 ± 8	89 ± 8	0.697	80 ± 8	80 ± 7	0.987
	W2	85 ± 7	85 ± 6	0.920	89 ± 7	89 ± 5	0.981	78 ± 8	80 ± 7	0.134
	W4	85 ± 8	86 ± 7	0.473	89 ± 9	90 ± 6	0.494	78 ± 8	80 ± 8	0.076
	ANOVA	Time × group interaction: $P = 0.271$			Time × group interaction: $P = 0.452$			Time × group interaction: $P = 0.175$		

SBP, systolic blood pressure; DBP, diastolic blood pressure; MINSBP, minimum systolic blood pressure; MINDBP, minimum diastolic blood pressure; MAXSBP, maximum systolic blood pressure; MAXDBP, maximum diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate. S, Screen (prior to treatment); B, baseline (prior to treatment); W1, W1, W4, weeks 1, 2 and 4 after treatment with either herbal (H, n = 67) or placebo (P, n = 66).

EXPERT OPINION

Norman M. Kaplan, M.D.

The University of Texas Southwestern Medical Center at Dallas

Dallas, TX

Herbal Ephedra/Caffeine for Weight Loss: A 6-Month Randomized Safety and Efficacy Trial

Boozer CN, Daly PA, Homel P, Solomon JL, Blanchard D, Nasser JA, Strauss R, Meredith T

Intl J Obesity 2002;25:593-604

After careful reviews of this manuscript, I do not believe that this study provides adequate data to assess the safety of marketed dietary supplements containing ephedrine alkaloids and caffeine for weight loss. Additional studies are needed to assess the safety of these products, especially large case/control studies comparing users versus non-users in the prevalence of various end-points such as incidence of hypertension, arrhythmias, coronary disease, and stroke.

The following factors have been considered:

- *Design and Duration of the Trial:* Adequate.
- *Subject Selection:* Appropriate. It should be noted that after appropriate initial telephone screening, more than 10% of the subjects who appeared eligible were excluded for medical reasons.
- *Inclusion/Exclusion/Dropouts/Withdrawal Criteria:* Appropriate and obviously much more stringent than feasible in clinical practice.

- *Endpoints:* Appropriately assessed.
- *Powering of the Study:* This is the major fault of this study. As the authors state, "A minimum of 66 subjects in each group would have been sufficient to detect a difference in [blood pressure and heart rate]." Only 46 subjects on ephedrine/caffeine and 41 on placebo completed the study.
- *Statistical Methods:* Appropriate.
- *Data Presentation:* Statistically significant effects on blood pressure and heart rate were noted but downplayed in the presentation and Discussion. The observed 4/4 mmHg difference in blood pressure, applied to a large population, could translate into a 20 to 40% increase in the incidence of strokes and myocardial infarction (see Prospective Studies Collaboration. *Lancet* 2002;360:1903-1913).

  Similarly, the observed heart rate difference of 6 bpm could translate into an increased prevalence of arrhythmias.

  In the Discussion, the ephedrine/caffeine group were said to have "decreased blood glucose." This is simply a reflection of a rise in blood glucose in the placebo group.
- *Applicability to Marketed Products:* This study examined effects of only a combination of ephedrine and caffeine and therefore may not be applicable to other marketed products.
- *Demographics:* The study population was obviously a carefully screened and healthy group. Only if the general population of potential users were required to undergo a similar careful assessment would it be appropriate to assume that they would have similar good and adverse effects.

- *Demographics, if Warning Label Not Followed:* The potential for adverse events would be even greater if the warning label restrictions were not followed.

I trust that the formulation of this opinion is what you requested.

Sincerely,

Norman M. Kaplan, MD

NMK:vlm

REVIEW
Food and Drug Administration
by
Richard L. Atkinson, M.D.
of
Boozer et al, Int J Obesity 26:593-604, 2003

Overall summary:

This paper is a well designed, well carried out evaluation of a dietary supplement (Metabolife) for the treatment of obesity. The conclusions reached by the authors are justified. The product produced statistically significant weight and fat loss with minimal side effects as compared to placebo over a six month period. However, the subjects were carefully selected to be free from medical conditions that might predispose to cardiac or vascular catastrophes. It is not possible to determine from this paper if untoward events may occur when the product is used by the general public, some of whom may have problems that contraindicate use of the pharmacologic agents contained in the product. Additional studies of at-risk subjects, carried out in a carefully controlled environment, such as a GCRC, would be needed to determine if the product predisposes to arrhythmias or cerebrovascular accidents. It may not be possible, ethically or practically, to perform such studies. Additional studies of an epidemiologic nature should be performed to determine if the risk of catastrophes on the product is increased. Attention should be paid to selecting a relevant control population to compare to consumers who use the product. Specifically, overweight and obese controls should be used for a comparison group.

An important caveat: After publication of the paper, the authors informed the International Journal of Obesity that there were questions about the contents of the active and placebo preparations. The principal author had attempted to check the levels of ephedrine and caffeine in the tablets, independent of the sponsors of the project. She discovered that about 1%, as best as can be determined, of the bottles were mislabelled by the sponsor. Not all of the bottles could be tested. The authors submitted a letter to the Editor with notification of this problem along with a comprehensive statistical evaluation of the possibility that the findings of the study might be invalidated. They concluded that the small number of errors was highly unlikely to invalidate the conclusions. However, in the absence of the ability of the authors to test all of the bottles used in the study, I believe it is impossible to rely on this study as a assessment of the safety and efficacy of the product. The study needs to be repeated with a similar design, with careful checking of all bottles to insure they contain the appropriate preparation.

Individual factor opinions:

1. Design and duration of the trial: The design of the trial was a randomized, double-blind, placebo controlled, prospective trial, the most valuable design available for testing pharmacologic agents. The primary outcome variables were body weight, body fat, and waist and hip circumferences. Safety was assessed by self-reported symptoms, laboratory testing, and highly sophisticated Holter monitoring equipment for cardiovascular parameters. The use of Holter monitors is extremely valuable in assessing cardiovascular risk, and is rarely used due to the time and expense necessary. Repeated Holter monitoring, especially during the first month, was a valuable tool for identifying any early risks of the product.

The duration of the trial was six months. This is sufficient time to determine if a weight loss agent will be effective and different from placebo. The study period is longer than most studies of other prescription and OTC agents for obesity currently on the market, many of which were studied for only three months (sibutramine and orlistat are exceptions). Most supplements on the market have not been tested at all, or if tested, have not been reported in the medical literature.

2. Subject selection, inclusion/exclusion: Subjects were recruited by standard methods and stringent criteria were used to exclude subjects at risk for medical conditions, including cardiovascular (CVD) and cerebrovascular (CBVD) conditions. However, smokers and diabetics under reasonable control, not on medications and with no evidence of CVD or CBVD were included. Subjects with hypertension and any subject with increased-risk abnormalities on either of two days of Holter monitoring were excluded. All subjects had a history and physical exam and extensive laboratory tests. Of 284 subjects screened, 167 were randomized to product or placebo. Thus, the subjects included in the study were a highly select group.

3. Dropouts/withdrawal criteria: Of 83 subjects randomized to product, 17 dropped out in the first month and 20 dropped out in the next 5 months, for a total of 37/83, or 45% total dropouts. Of 84 subjects randomized to placebo, 17 withdrew in the first month and 26 dropped out in the next 5 months, for a total of 43/84, or 51% total dropouts. The most common reason for dropout was subject choice. A few subjects dropped out for noncompliance or protocol violations. Ten subjects on product and 11 placebo subjects were dropped for cardiovascular complaints; not significantly different. One subject on placebo had gallbladder surgery and one on product had an elevated creatinine. Overall, the withdrawal criteria were reasonable, and there were no difference or even any apparent trends for differences between adverse events or reasons for dropouts. It should be noted that several minor adverse events, including constipation, dry mouth, heartburn, insomnia, and upset stomach were increased in the

product group, particularly during the first four weeks. These symptoms apparently did not lead to an increased dropout rate in the product group.

4. Endpoints: The endpoints were body weight, body fat, body circumferences, and safety measures. These were all relevant and important. I cannot identify other important endpoints that would have been more useful. The study showed that change in several important endpoints that concern obesity investigators were different between product and placebo. As compared to placebo, product had beneficial and significant effects on body weight, body fat, body circumferences, LDL cholesterol, HDL cholesterol, and glucose. Several blood pressure and pulse parameters were less favorable on product, including systolic and minimum systolic blood pressure, and pulse rate, although these differences were clinically insignificant, and in the range of differences produced by sibutramine, a prescription obesity agent.

It should be noted that in Figure 2, body weight is still declining at a fairly steep slope, suggesting that maximum weight loss had not occurred. Data from Astrup's group in Denmark showed that higher doses of ephedrine and caffeine produced weight losses of about 16% of initial body weight. Stock et al demonstrated that even after weight loss stopped, body fat continued to decline and muscle mass increased, suggesting that this combination acts on beta-3 receptors.

5. Powering of the study: I am not a statistician and cannot comment in depth on the power analysis of this study. My simple power analyses on major outcome variables suggested that the study had sufficient power to detect differences of importance. Moreover, the very similar outcomes of major cardiovascular risk factors, as determined by Holter monitoring, suggest that any additional risk of CVD or CBVD events in populations similar to the study population must be extremely small.

6. Statistical methods: I am not a statistician and can only comment that the statistical methods appear appropriate and the analyses well performed.

7. Data presentation: The paper is written very clearly and the data are presented as both completer analysis and last visit carried forward, the standards for such studies.

8. Applicability of the study and formulation to marketed products: This paper describes a research protocol. The subject population was carefully chosen and although these subjects may be generally representative of the population of consumers who seek weight loss by dietary supplements, there are important differences. The population was chosen for absence of contraindications to treatment with ephedrine and caffeine, and all were carefully screened. Only 58% of screened subjects were

randomized in the protocol; the other 42% either did not choose to participate or had reasons they could not participate. This protocol may not be as representative of the general population of overweight and obese subjects as the subjects of other weight loss trials because the initial evaluation was so comprehensive. However, the lack of major complications and similarity of the adverse events to placebo, suggests that the combination of ephedrine and caffeine is not as dangerous as has been made out by the media and trial lawyers.

The study formulation may be somewhat different than the preparations that are marketed by the Metabolife company. The manuscript states that ephedrine and caffeine were the only "active" ingredients. Brochures on Metabolife weight loss product list many additional ingredients such as bee pollen, ginseng, goldenseal, ginger, and others. It is unlikely that the additional ingredients had any effect on body weight or composition, but any adverse effects from single agents or the combination are unknown. If the preparation used in the study is not the same as the marketed product, this also limits the conclusions one can draw from this paper. Effectiveness is likely to be similar since the authors almost certainly are correct that the active ingredients are ephedrine and caffeine. However, the safety of the additional products is unknown.

9. Study demographics vs demographics of consumers who follow the label instructions: As noted above, the study subjects may be different than the average consumer who buys the product. However, surveys done at the time of phen-fen, by the Interneuron company and by an independent physician commissioned by the State of Texas concluded that less than 5% of people who used phen-fen did not qualify under the FDA guidelines. Thus, it is likely that people who use this product have medically significant overweight and may benefit from weight loss and improvements in complications of obesity as shown in the study. If all people who purchase the product follow the warnings on the labels, it seems unlikely that there would be a great deal of additional risk in these patients.

10. Study demographics vs demographics of consumers who ignore the label: It is likely that people who should not be using this product because of the presence of disease that would have precluded participation in the study may buy the product and use it without medical or other supervision. It is not clear if such individuals would be at increased risk of adverse events or sudden death, and additional studies would be needed to determine the degree of this risk. The hostile legal environment for obesity agents, and particularly for combinations of ephedra or ephedrine and caffeine, probably would preclude doing studies of individuals at higher risk than in this study. Such studies would need to be done on a research unit such as a GCRC where subjects would be carefully and continually monitored. It is not clear if such studies would be approved by an IRB, although there

appears to be little actual scientific data to preclude such studies.

Historical interventions for obesity, such as very low calorie diets (VLCD) were routinely condemned in the press and even by the FDA in absence of firm data to support such condemnation. When studies were actually done with high quality VLCD products in "high risk" patients such as those with angina, significant improvements in symptoms and cardiovascular performance were seen. More recent research has documented the dramatic increases in health risk from obesity, and it is possible that weight reduction, which has been repeatedly shown to reduce health risks, may produce benefits that outweigh the dangers of ephedrine and caffeine.

If prospective, intervention trials cannot be done, the FDA and/or NIH might consider funding epidemiologic studies to determine if the numerous anecdotes about the dangers of ephedrine and caffeine actually hold up to scientific scrutiny. The use of anecdotes to formulate public policy is difficult to justify from a scientific point of view. Although thousands of anecdotes have been reported to the FDA and in the medical literature on adverse events, such as myocardial infarctions, strokes, and sudden death, the denominator for such populations is not known.

An instructive example of the use of anecdotes is the recent removal of phenylpropanolamine from the market. Anecdotal data were used to conclude that the risk of strokes in people on PPA was increased. The analysis of the data by investigators from Yale Medical School factored in many covariates, but obesity did not appear to be one of them. It is clear that obesity is a major risk factor for myocardial infarctions, strokes, and sudden death. The population of individuals who use drugs such as PPA or ephedrine-caffeine are highly enriched for overweight and obesity. Analyses of reference populations that do not account for overweight and obesity are inappropriate. Prevalences or incidences of adverse events in the general population are not suitable reference points for frequency of such events in overweight and obese people.

11. Recommendations for future studies: My personal recommendations are:

a. Repeat the Boozer et al study: The study is severely compromised by the finding that some bottles (about 1%) labelled as placebo actually contained active agents, and vice versa. While the authors have provided a comprehensive statistical analysis of the data and conclude that this small degree of error does not invalidate the findings, this conclusion rests upon the assumption that the true error rate of mislabelling was only 1%. The study was very well designed and carried out. A repeat study that obtained similar results would give strong support for

the efficacy and safety of the product in a population defined by the label recommendations.

b. Assess people at higher risk of cardiovascular risk: It is possible that the weight loss from the product would be sufficient to outweigh the potential adverse events that are postulated to occur with the product. Very carefully done studies in an intensively followed population, ideally on a GCRC, might determine if current perceptions of the dangers of ephedrine and caffeine are overestimated or are accurate.

I personally believe that overweight and obese individuals who use ephedrine and caffeine should be followed by a physician until such time as this combination has been shown to be safe for over the counter use. Current options for the treatment of obesity are very limited. If ephedrine and caffeine are effective, as Astrup et al's data and others suggest, it would be undesirable to see this removed from the market. It would be doubly unfortunate if the combination had not been given a fair trial and was removed based solely on anecdotal evidence.

c. Epidemiologic studies: To obtain valid epidemiologic studies, it will be necessary to characterize the population of overweight and obese controls better. One study that might be done would compare in a prospective fashion all people who died of cardiovascular and cerebrovascular disease in a large population such as one or more large cities or states. Blood or tissue could be obtained for the presence of ephedrine and caffeine from all patients dying of these disorders, and a history taken, where possible, for the use of these agents at some fixed interval before death. The remainder of the population, matched for age and BMI, but without a history of consumption of ephedrine and caffeine, and without these agents in blood or tissue would serve as a control. Random telephone surveys to obtain height and weight and to assess the use of ephedrine-caffeine products could be conducted to estimate the denominator. This design would determine if there is a higher death rate in overweight and obese people who use ephedrine-caffeine than in such people who are not using the combination.

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Department of
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SECTION ON BIOSTATISTICS

Charles Prettyman
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April 9, 2003

Mr. Prettyman;

Attached is my review of Boozer et al., Intern J Obesity 2002;26:593-604. Please let me know if I can further address any areas of otherwise be of assistance.

Sincerely,

Mark Espeland, PhD, FASA
Professor of Public Health Sciences
Sections on Biostatistics and Epidemiology
Wake Forest University Health Sciences

Re: Boozer CN, Daly PA, Homel P, Solomon JL, Blanchard D, Nasser JA, Strauss R, Meredith T. Herbal ephedra/caffeine for weight loss: a 6-month randomized safety and efficacy trial. International Journal of Obesity 2002;26:593-604.

Summary

The clinical trial described in this manuscript is of insufficient size and duration to establish the safety of a specific and standardized ephedra/caffeine preparation when taken according to protocol. In a broader sense, it therefore fails to establish safety across a range of products of varying dose and composition with unsupervised use.

Design and Duration of the Trial

The manuscript describes a randomized, double-blind, clinical trial with up to six months of follow-up. Participants were assigned, with equal probability to either active or placebo therapy consisting of two tablets, three times a day (six tablets per day, total). Active tablets included herbal ma huang and kola nut, formulated to contain 15 mg total ephedrine alkaloids and 32 mg caffeine. All participants received a modest counseling on diet and exercise throughout follow-up.

Subject Selection

Volunteers were solicited through newspaper advertisements and flyers. Enrollment involved a telephone interview, medical screening, and a baseline evaluation to determine eligibility and collect pre-treatment data.

Inclusion/Exclusion/Dropouts/Withdrawal Criteria

Participants were required to be between 18 and 80 years of age and have a body mass index between 25 and 40 kg/m^2, inclusive. Individuals with diabetes were eligible only if their hemoglobin A1c levels were controlled without medications. Addition exclusion criteria included poor health, pregnancy or nursing, recent weight loss, recent participation in other diet or drug studies, and self-reported daily caffeine consumption greater than 500 mg/day.

Overall, 167 participants were randomized in the trial (84 to placebo and 83 to active therapy). Within 4 weeks of randomization, 34 participants withdrew (17 in each arm). The major reason for early withdrawal from the placebo arm was participant choice (9 of 17); the major reasons for early withdrawal from the active therapy were a cluster of cardiovascular and central nervous system symptoms. After four weeks, an additional 26 participants withdrew from the placebo therapy and 20 participants withdrew from active therapy; during this period, the most frequent reason for withdrawal from both arms was individual choice. Overall, 41 of the 84 participants assigned to placebo therapy (49%) completed the planned six months of follow-up; 46 of 83 participants assigned to active therapy (55%) completed follow-up.

Participants were withdrawn by investigators for protocol violations (previously undisclosed ineligibility: N=3 herbal therapy and N=4 placebo), noncompliance (N=4 herbal therapy and N=3 placebo), and for potential adverse effects (N=13 herbal therapy and N=10 placebo group). The adverse effects included elevated blood pressure,

irregular heart beat, multifocal ventricular events, ventricular events, and ventricular runs of five or more, and were evenly distributed between the treatment groups.

Collection of endpoint data was apparently terminated on participants who were withdrawn from the study.

Endpoints

Efficacy was assessed based on measured changes in body weight, body fat, and girths (waist and hip). Safety was assessed based on measured changes in cardiovascular parameters (EKG, blood pressure, and pulse), blood analytes (serum glucose, cholesterol, triglycerides, electrolytes, TSH, and CBS), liver enzymes (creatinine, ALT, AST) and changes in self-reported symptoms and reasons from study withdrawal. In addition, a urine toxicology screen was performed. Process measures included self-reports of dietary intake and activity levels.

Powering of the Study

The study was powered to detect a mean difference of 4.1 mmHg systolic and 4.6 mmHg diastolic blood pressure and a mean difference of 6 bpm heart rate at Week 4 using uncontrolled t-tests. These calculations were used to support the decision to accrue at least N=66 per group at the end of the acute phase (Week 4). The authors state that power calculations were "primarily concerned with the possibility of adverse effects during the acute phase of the study..." however no calculations are presented to indicate either the anticipated prevalence or targeted relative risk of adverse events that would be detected. Indeed, the sample size of N=66 per group is associated with a 90% statistical power to detect differences in incidences as large as 0.29 (e.g. 0.35 vs 0.64): thus, there is not sufficient power to detect fairly marked increases in adverse event rates, even in uncontrolled analyses. For example, an observed doubling of risk of an adverse event between active and placebo arms of 10% to 20% would not be statistically significant and the study would have little chance of detecting an underlying effect size of this magnitude.

Overall, it is estimated that the study provided about 28 person years of follow-up in the active treatment arm (and similar amounts of follow-up in the placebo arm). This limited experience provides virtually no opportunity to detect and contrast many types of serious adverse events.

Statistical Methods

Means were compared by repeated measures analysis of variance and by t-tests. Rates of events were compared by weighted least squares methods and chi square tests. More comprehensive approaches would use contrasts from the repeated measures techniques for pairwise comparisons at specific time points and control for type I error. Maximum likelihood approaches for the continuous data, rather than least squares methods, would also provide better protection against biases associated with missing data [e.g. Little. 1992].

Of concern was the decision to use last observation carried forward method, in which missing data were imputed as being equal to previous measurements. This approach is based on a model for missing data mechanisms that is difficult to defend and can markedly bias estimates of means, variances, and longitudinal correlations [Miller, 2001].

While the authors state that they used an intention to treat approach, the apparent failure to pursue data collection on participants that were "withdrawn" from the study (in some cases due to non-adherence) is not consistent with this approach and conforms more closely to an adherer's only approach. Missing data were imputed to correspond to data that were collected prior to when participants were withdrawn.

The overall approach to the statistical analysis is unsatisfactory and does not give a clear picture to the consequences on six month outcomes of initiating the herbal mixture in a cohort of individuals. It also fails to address any consequences associated with cessation of herbal therapy.

Data Presentation

The reported impact of herbal therapy on weight is consistent with a recent comprehensive meta-analysis of such compounds [Sheckelle, 2003], which indicated that ephedra/caffeine combinations are associated with modest weight losses over 6 months. The current manuscript indicates that body fat, hip circumference, and waist circumference were also modestly reduced among adherers to active therapy. There was little difference in blood pressure, as measured at office visits, that was associated with therapy, however heart rate was modestly increased. With 24-hour blood pressure monitoring, there appeared to be slight increases in average systolic and diastolic blood pressure among participants assigned to the herbal therapy relative to placebo, but little difference in either maximum or minimum blood pressures. Little difference was found between treatment groups in measures (other than heart rate) collected from Holter monitors. Minor, but nominally significant, favorable changes in HDL and baseline glucose were associated with herbal therapy.

Herbal therapy was associated with increased reporting of the following symptoms during at least one follow-up period: constipation, concentration, dizziness, dry mouth, heartburn, insomnia, anxiety, and upset stomach. As noted above, these comparisons may be compromised by the analytical approach adopted by the investigators.

Applicability of the Study and Formulation to Marketed Products

The herbal preparation used in this research study was a standardized mixture of Ma Huang and Kola nut targeted to contain 15 mg of total ephedrine alkaloids and 32 mg of caffeine. Marketed herbal products vary in the doses of these two analytes and often contain other potentially active agents. Study participants adhering to the protocol were to take six tablets a day, for a total of 90 mg ephedrine alkaloids and 196 mg of caffeine. For contrast, Metabolife 356 has labeling limiting intake to a maximum of 96 mg ephedrine alkaloids and 320 mg caffeine (and also contains vitamins, minerals, and other herbal products). Twinlab "Ripped Fuel" has labeling limiting intake to 120 mg ephedrine alkaloids per day and 120 mg of caffeine (and also contains chromium and L-carnitine). The extrapolation of study results to these and other like products is not direct, however it is to be expected that any safety issues associated with ephedrine alkaloids extend across a range of doses.

Study Subject Demographics vs Demographics of Population of Users Recommended by Included Labels

The study subjects were recruited through their interest in weight loss and screened to exclude those with hypertension and/or evidence of cardiac disease. Use of herbal products in the general population is unsupervised, however labeling of several products warn against use by individuals with high blood pressure or heart disease. In general, participants in clinical trials tend to be more highly educated and have better access to care than the general population. The study subjects were not representative of individuals who take herbal ephedra in an attempt to increase athletic performance.

Study Subject Demographics vs Potential Population if Warning Label Is Not Followed

Use of the product contrary to warning labels would involve individuals with existing heart disease and high blood pressure.

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